UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,850	12/14/2001	Patrick M. Hughes	D-3004	7435

33197 7590 10/18/2004

STOUT, UXA, BUYAN & MULLINS LLP
4 VENTURE, SUITE 300
IRVINE, CA 92618

EXAMINER	
SPIVACK, PHYLLIS G	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 10/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/016,850	HUGHES ET AL.	
	Examiner	Art Unit	
	Phyllis G. Spivack	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *7 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8, 9, 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants' Amendment filed July 9, 2004 is acknowledged. Claims 1-16 remain under consideration wherein the therapeutic component is a quinoxaline compound. Claims 7 and 10 remain withdrawn from consideration by the Examiner, 37 CFR 1.142(b), as directed to non-elected inventions. The subject matter presently under consideration remains those pharmaceutical conjugates of claims 1-6, 8, 9 and 11-16, wherein the therapeutic component is a quinoxaline compound of instant claim 8.

It is noted the subject matter of claim 12 in U.S. Patent 6,562,873 encompasses that of instant claims in that alpha-2 adrenergic agonists may be a therapeutic component. A "composition" encompasses a conjugate. The open language of the present claims allows for the inclusion of additional active agents.

Claims 1-6, 8, 9 and 11-16 were rejected under 35 U.S.C. 112, second paragraph, in the first Office Action as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention with respect to the term "general" in the description of formula A.

Subsequent to the deletion of the term, this rejection of record is withdrawn.

In the last Office Action claims 1-6, 8, 9 and 11-16 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed to pharmaceutical conjugates comprising a quinoxaline compound of instant claim 8, an efficacy enhancing component of formula A that is, for example, memantine, wherein any of the R terms may be a C_1-C_{10} hydrocarbon. Claim 14 requires the

pharmaceutical conjugate to have an aqueous solubility and a partition coefficient and/or an affinity for melanin that is greater relative to a compound comprising the same therapeutic component that is not joined to an efficacy-enhancing component. The specification provides support for various pharmaceutical conjugates none of which comprise a quinoxaline compound of instant claim 8, an R term that is a C_1-C_{10} hydrocarbon nor data to support an aqueous solubility and a partition coefficient and/or an affinity for melanin that is greater relative to a compound comprising the same therapeutic component that is not joined to an efficacy enhancing component.

It was asserted the instant specification fails to provide guidance that would allow the skilled artisan background sufficient to practice the instant invention without resorting to undue experimentation. Each particular therapeutic component has its own specific characteristics and physical/chemical properties. The broad recitation "a pharmaceutical conjugate comprising a therapeutic component and an efficacy enhancing component" is inclusive of a plethora of diverse compounds.

Applicants argue one of ordinary skill in the art would be able to prepare the claimed invention and enablement is not precluded by the necessity for some experimentation such as routine screening.

The Examiner is generally in agreement with these points with respect to the elected species; however, the working examples are limited to conjugates of bromonidine, insulin-like growth factor-1, ketoconazole, ciloxan and ganciclovir, all of which are ophthalmic drops. Preparation of the elected species is not disclosed.

Applicants have failed to provide guidance relating to the requirement of the pharmaceutical conjugate to have an aqueous solubility and a partition coefficient and/or an affinity for melanin that is greater relative to a compound comprising the same therapeutic component that is not joined to an efficacy-enhancing component.

In view of the plethora of functionalities encompassed in "a therapeutic component" in claims 1 and 16, the specification does not reasonably provide enablement for the preparation of any therapeutic component conjugated to the efficacy enhancing component depicted by formula A. The rejection of claims 1-6, 8, 9 and 11-16 under 35 U.S.C. 112, first paragraph, is maintained.

Claim 8 was rejected in the last Office Action under 35 U.S.C. 112, both first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make the invention, and for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

Applicants failed to particularly point out the definition of "derivatives" of the recited quinoxaline compounds. The metes and bounds of "derivatives" cannot be precisely determined.

Applicants argue a derivative of quinoxaline is an agent that is not structurally identical to quinoxaline but functions similarly to quinoxaline.

It is noted the cited examples on pages 9-10 are structurally the same. They are precisely quinoxaline, not derivatives.

The rejection of claim 8 is maintained for the reasons of record.

Claims 1-6, 8, 9, 11-13, 15 and 16 were rejected under 35 U.S.C. 103(a) as being unpatentable over both Desantis, L., US 2001/0047012, and Collins et al., WO 01/92288, in the last Office Action. It was asserted Desantis teaches combination therapy for treating glaucoma comprising administering a glutamate antagonist and an intraocular pressure-lowering compound. Brimonidine, 5-bromo-N-(4,5-dihydro-1H-imidazole-2-yl)-6-quinoxalinamine, a compound of instant claim 8, is a preferred intraocular pressure-lowering compound and memantine is a well established glutamate antagonist. See page 2, paragraphs [0018] and [0023]. Application to the eye encompasses topical administration. Collins teaches various pharmaceutical conjugates comprising a bioactive agent that is covalently bound directly or indirectly to a linker. Efficacy enhancing components of formula A are disclosed on page 92. Therefore, in view of the combined teachings of Desantis and Collins, one skilled in the art of formulation chemistry who seeks a pharmaceutical conjugate comprising a therapeutic component and an efficacy enhancing component of instant formula A would have been motivated to prepare a formulation comprising two known therapeutically effective ophthalmic agents in a formulation that is a conjugate to treat ocular pathologies.

Applicants argue there is no motivation provided to combine the teachings of the references to obtain the claimed conjugates. Applicants urge the agents are separate from each other in the Desantis reference. In the Collins reference Applicants argue amantadine is disclosed to be a therapeutic component, not an efficacy-enhancing

component, while the efficacy-enhancing component has a completely different chemical structure.

Applicants' arguments have been given careful consideration but are not found persuasive. The rejection of claims 1-6, 8, 9, 11-13, 15 and 16 is repeated for the reasons of record.

1-Aminoadamantane analogues such as memantine are established in the prior art as useful agents for conjugation with poorly soluble drugs. Such conjugates provide chemical stability and are known to dissociate under physiological conditions. Desantis establishes a therapeutic advantage of combining known ophthalmic drugs such as memantine and brimonidine. Collins teaches pharmaceutical conjugates with a low molecular weight linker to which a bioactive agent may be covalently bound. The intended uses, as defined in claim 1 as "a therapeutic component" and "an efficacy enhancing component", confer no patentable weight to composition claims. The applied references teach the combination of a compound of instant formula A with various therapeutic agents. The specification fails to define a "conjugate" as anything more than a combination of compounds wherein increased solubility or bioavailabilty is sought.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this Final Action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication should be directed to Phyllis G. Spivack at telephone number 571-272-0585.

Phyllis Spivack

Phyllis G. Spivack
Primary Examiner
Art Unit 1614

October 14, 2004

PHYLLIS SPIVACK
PRIMARY EXAMINER